CMDh/223/2005
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Public Assessment Report

Scientific discussion

Vistale 0.3 mg/ml + 5 mg/ml eye drops, solution in single-dose container

(bimatoprost/timolol)

ES/H/0934/001/DC

Date: 20/10/2025

This module reflects the scientific discussion for the approval of Vistale 0.3 mg/ml + 5 mg/ml eye drops, solution in single-dose container. The procedure was finalised at 28/05/2025. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Vistale 0.3 mg/ml + 5 mg/ml eye drops, solution, in single-dose container, from Laboratorios Salvat S.A.
The product is indicated for: Reduction of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.
A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10 (3) of Directive 2001/83/EC."

II. QUALITY ASPECTS

II.1 Introduction

The finished product is presented as eye drops, solution in single dose container. It contains 0.3 mg/mL of bimatoprost and 5 mg/mL of Timolol (as 6.8 mg Timolol maleate) as active substances. The maximum daily doses are 20 µg of bimatoprost and 0.33 mg of Timolol.
The product is available in clear LDPE containers with a twist-off tab, placed in aluminium foil pouches, within a carton box.

II.2 2.2Drug Substance

Bimatoprost

Bimatoprost is a known active substance not described in the Ph.Eur. The ASMF procedure has been used to provide the quality information of this active substance.

General Information

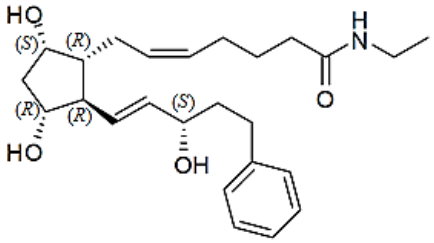
Nomenclature:

INN: Bimatoprost

Chemical name: (Z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[(1E,3S)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-N-ethyl-5-heptenamide.

CAS-No: 155206-00-1

Structure:



MW: 415.57

Chemical formula: C25H37NO4

General Properties: White or almost white, crystalline powder, very soluble in Ethanol and slightly soluble in Water.
Bimatoprost shows specific rotation due to the presence of five asymmetric carbons.
A consistent polymorphic form, characterised by PXRD, is obtained by the manufactrer.

Manufacture, process controls and characterisation

The description of the manufacturing process is properly detailed. The specifications of the materials used in the synthesis are sufficient and adequate. The profile of impurities, including residual solvents, of these materials which can influence the quality of the active substance are well defined and controlled. The acceptance criteria for the critical stages and the information on the quality and control of intermediates are adequate.

Specification, analytical procedures, batch analysis

Active substance specifications are considered appropriate and limits justified. Analytical methods are correctly described and validation carried out according to ICH. Batch results support consistent production.

Container closure system

The choice of the container closure system is properly justified. Compliance with the relevant requirements and/or regulations is confirmed.

Stability

Stability studies have been performed in accordance with current guidelines. Protocol, controlled parameters and test methods are considered adequate. The packaging material is similar to that proposed for storage. Proposed re-test period and storage conditions are justified.

Timolol maleate

Timolol maleate is a known active substance described in the Ph.Eur. The CEP procedure has been used to provide the quality information of this active substance.

General Information

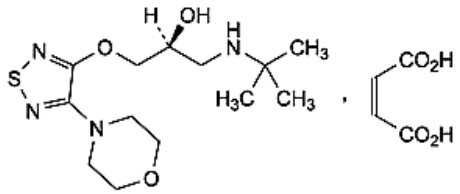
Nomenclature:

INN: Timolol maleate

Chemical name: (2*S*)-1-[(1,1-Dimethylethyl)amino]-3-[[4-(morpholin-4-yl)-1,2,5-thiadiazol-3-yl]oxy]propan-2-ol (*Z*)-butenedioate

CAS-No: 26921-17-5

Structure:



MW: 415.57

Chemical formula: $C_{17}H_{28}N_4O_7S$
$C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$

General Properties: White or almost white, crystalline powder or colourless crystals. Soluble in water and in ethanol (96 per cent).

Manufacture, process controls and characterisation

As CEP procedure is used, information on manufacture, process controls and characterisation of the active substance has been assessed by EDQM.

Specification, analytical procedures, batch analysis

Active substance specifications are in accordance with Ph. Eur. Monograph.

Container closure system

As CEP procedure is used, information on packaging material of active substance has been assessed by EDQM.

Stability

Re-test period is included in the CEP. Stability studies have been assessed by EDQM.

II.3 Medicinal Product

Description of the product

The medicinal product consists of eye drops solution in single dose container. The solution is colourless to sligghtly yellow solution and contains 0.3 mg/mL of bimatoprost and 5 mg/mL of Timolol (as 6.8 mg Timolol maleate) as active substances and includes sodium chloride, tribasic sodium phosphate dodecahydrate and water for injections as excipients.

The solution is packed in a LDPE container with a twist-off tab, placed in aluminium foil pouches and within a carton box.

Pharmaceutical Development

The development of the product has been described, the choice of excipients is justified and their functions explained.

The physicochemical characteristics of the active substance that may affect the pharmaceutical form are identified and their control strategy is justified.

The proposed method of sterilization has been appropriately justified.

Manufacture of the product
The manufacturing process is fully described and in-process controls are appropriate considering the nature of the product and the manufacturing process. The industrial batch size is well-defined.
Sufficient validation data are.
Excipients
Excipients used are well known and of appropriate quality.
None of the excipients is of animal origin.
Product specification, analytical procedures, batch analysis
The finished product specifications are adequate to control the finished product. Provided description and validation data for the analytical methods are adequate. Batch analysis data have been submitted and the results show that the finished product meets the proposed release specification.
Container closure system
The finished product is packaged in a LDPE container with a twist-off tab, placed in aluminium foil pouches and within a carton box. The choice of the container closure system is justified considering the nature of the finished product and manufacturing process. Compliance with the relevant requirements and/or regulations is confirmed.
Stability
Stability studies have been performed in accordance with current guidelines. The proposed protocol is considered adequate. The packaging material is the same as that intended for marketing. Proposed shelf-life and storage conditions are properly established.

Shelf-life: 30 months.
Storage conditions: This medicinal product does not require any special temperature storage conditions. Store the single-dose containers in the pouch and return the pouch to the carton to ensure protection.
In-use shelf life: Once the aluminium pouch is opened, the single-dose container should be used within 30 days. Discard the single dose container immediately after use.

III. NON-CLINICAL ASPECTS

III.1 Critical evaluation of the Non-Clinical Overview

Pharmacodynamic, pharmacokinetic and toxicological properties of bimatoprost and timolol are well known. As bimatoprost and timolol are widely used, well-known active substances, the applicant has not provided additional studies, and further studies are not required. Overview based on literature review is, thus, appropriate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

The approval of the product will not change the total quantity of bimatoprost and timolol released in the environment. Therefore, additional ERA studies are not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

Bimatoprost and bimatolol are a well-known actives substances with established efficacy and safety. A clinical overview has been provided, which is based on scientific literature. The clinical overview justifies that there no need to generate additional clinical data.

The PI documents has been amended according to the RMS and CMSs comments, and it is fully aligned with the reference product and the guidelines of application.

IV.2 Pharmacokinetics

Biowaiver

The qualitative and quantitative composition of Bimatoprost 0.3 mg/mL and timolol 5mg/mL eye drops solution and the reference product Ganfort is essentially similar (identical with respect to actives and excipients except sodium hydroxide, hydrochloric acid and citric acid monohydrate used only in the reference product for pH adjustment).
Both products contain the same type of aqueous solution, and both are available in the same pharmaceutical form (eye drops solution in single-dose container).
Comparison of physicochemical properties indicate in vitro similarity of applied product and reference product.

Considering the concerned eye drops constitute an aqueous solution, which has an essential similar qualitative and quantitative composition as the reference product and displays essentially similar physiochemical properties, the justification for a biowaiver is acceptable.

IV.3 Pharmacodynamics

No new studies on pharmacodynamics have been submitted, which is acceptable for this hybrid application.

IV.4 Clinical efficacy

No new studies on pharmacodynamics have been submitted, which is acceptable for this hybrid application.

IV.5 Clinical safety

No new studies on pharmacodynamics have been submitted, which is acceptable for this hybrid application.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to

identify, characterise, prevent or minimise risks relating Vistale 0.3 mg/ml + 5 mg/ml eye drops, solution in single-dose container.

There are neither proposed additional pharmacovigilance activities nor proposed additional risk minimisation measures planned for Vistale 0.3 mg/ml + 5 mg/ml eye drops, solution in single-dose container.

IV.7 Discussion on the clinical aspects

Described in section IV.2.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the hybrid product Vistale 0.3 mg/ml + 5 mg/ml eye drops, solution in single-dose container is found adequate. There are no objections to the approval of Vistale 0.3 mg/ml + 5 mg/ml eye drops, solution in single-dose from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.